REMARKS

Claims 1-21 and 23-80 were pending and claims 1-21, 25-29, 67-72 and 80 were under consideration in the application. Claims 23, 24, 30-66 and 73-79, withdrawn from consideration as directed to non-elected inventions, have been canceled without prejudice. Claims 1, 67 and 80 have been amended. New claims 81 and 82 have been added.

Claim 1 was amended to recite a functional limitation and to change the level of homology. Claim 67 was amended to further clarify the claim language. Claim 1 was amended to recite a functional limitation.

New claims 81 and 82 were added further specifying a functional limitation.

No new matter has been added.

Priority

The Office Action alleges that the present application is not "entitled to the benefit of the filing date of US provisional application 60/225,262 as it does not satisfy the utility/enablement requirement of 35 U.S.C 101/112 first paragraph" (citing the July 17, 2003 Office Action). Applicants do not agree.

As will be discussed in greater detail below in relation to the rejection under 35 U.S.C. §§ 101, 112, 102 and 103, both the present application and US provisional application 60/225,262 satisfy the utility and enablement requirements of 35 U.S.C §§ 101 and 112, first paragraph. Also, Applicants respectfully assert that several of the references cited against the present application confirm that the present application complies with the utility and enablement requirements of 35 U.S.C §§ 101 and 112, first paragraph.

Rejection under 35 U.S.C. § 101

Claims 1-21, 25-29 and 67-72 remain rejected and claim 80 is newly rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a specific, substantial and credible asserted utility or a well established utility. The Office

alleges that the arguments presented by Applicants in response to the previous Office Action, although considered, were not deemed persuasive because, *inter alia*, "the issue is not whether GPCRS as a whole have any utility, rather, the issue is that the presently claimed nGPCR-1079 does not have a substantial, and specific, or a well-established utility." (Office Action, page 3). The Office also asserts that that Applicants' arguments comparing the utility of DNA ligases to the utility of GPCRs were unpersuasive. For example, the Office states that "the situation in GPCRs is completely different from that of DNA ligases because the main function of DNA ligases is to ligate DNA regardless of different molecules of DNA ligases, whereas GPCRs are extremely diverse with respect to their functional properties." (Office Action, page 4). Applicants respectfully disagree.

The specification recites that the claimed receptor is a GPCR and is useful, *inter alia*, in the treatment of sexual dysfunction and hormonal disorders, and is discussed, *inter alia*, in paragraphs [00140], [00193], and [00200] of the application as filed. As set forth below, the claimed receptor is a G protein-coupled receptor affecting testicular descent (GREAT). GREAT receptors are known to play significant roles in disorders relating to hormonal disorders and sexual dysfunction. Therefore, specific, substantial and credible utilities exist for the claimed receptors.

Utility Examination Guidelines

The Utility Examination Guidelines (the "Guidelines") require that a claimed invention have a specific, substantial and credible asserted utility, or, alternatively a well-established utility. The claimed receptors are useful, *inter alia*, to treat and diagnose disorders relating to sexual dysfunction and hormonal disorders. The claimed receptors share at least 97% sequence homology with two GREAT receptors, a subfamily of GPCRs.[1] The fact that the claimed receptors share such significant sequence homology with receptors with a known function supports the assignment of the same specific, substantial, and credible utilities of GREAT receptors to the claimed receptors. The

[1] See BLAST alignment, NCBI Sequence Viewers (2), Gorlov *et al.*, Hum. Mol. Genet. 11 (19), 2309-2318 (2002), and Hsu *et al.*, Science 295 (5555).

utilities asserted are art-established: those skilled in the art would readily acknowledge that the claimed receptors are useful within the meaning of 35 U.S.C. § 101.

As Applicants have asserted utilities that are specific, substantial and credible, and well established, the Utility Requirement has been satisfied. Applicants therefore respectfully request the withdrawal of the rejection under 35 U.S.C. § 101.

Under the Guidelines, Office personnel are instructed to review the specification and claims of the application to determine if a specific and substantial utility that is credible is present. The Guidelines note that the specific and substantial requirement "excludes 'throw-away', insubstantial,' or 'nonspecific' utilities, such as the use of a complex invention as landfill." The Guidelines go on to note that an Examiner's "*prima facie* showing ***must*** establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial." "If the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do ***not*** impose a rejection based on lack of utility." (Guidelines, emphasis added).

The Guidelines comment on the use of computer based analysis of nucleic acids to assign functions to a nucleic acid or polypeptide based upon homology to sequences found in databases. Specifically, the Guidelines state that the:

> suggestions to adopt a *per se* rule rejecting homology based assertions of utility ***are not adopted***. An applicant is entitled to a patent to the subject matter claimed unless statutory requirements are not met (35 U.S.C. 101, 102, 103, 112) . . .The inquiries involved in assessing utility are fact dependent, and the determinations must be made on the basis of scientific evidence. Reliance on the commenters' *per se* rule, rather than a fact dependent inquiry, is impermissible because the commenters provide no scientific evidence that homology-based assertions of utility are inherently unbelievable or involve implausible scientific principles. *See, e.g., In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (rejection of claims improper where claims did 'not suggest an inherently unbelievable undertaking or involve implausible scientific principles' and where ''prior art * * * discloses

> structurally similar compounds to those claimed by the applicants which have been proven * * * to be effective').
>
> A patent examiner ***must*** accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The examiner's decision must be supported by a preponderance of all the evidence of record. *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." *Fujikawa* v. *Wattanasin,* 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). The Office will take into account both the nature and degree of the homology.
>
> When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein. If the preponderance of the evidence of record, or of sound scientific reasoning, casts doubt upon such an asserted utility, the examiner should reject the claim for lack of utility under 35 U.S.C. 101. For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class. When there is a reason to doubt the functional protein assignment, the utility examination may turn to whether or not the asserted protein encoded by a claimed nucleic acid has a well-established use. If there is a well-established utility for the protein and the claimed nucleic acid, the claim would meet the requirements for utility under 35 U.S.C. 101. If not, the burden shifts to the applicant to provide evidence supporting a well-established utility. There is no *per se* rule regarding homology, and each application must be judged on its own merits.

(Guidelines; emphasis added).

Preliminarily, Applicants remind the Office that specific and substantial utilities have been provided for the claimed receptors and that the asserted utilities are credible to the art-skilled. The Office has failed to provide any evidence that "it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial."

The Utility requirement may also be satisfied by an "Art Established Utility" which means that "a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention... and the utility is specific, substantial and credible." (M.P.E.P. §2107).

The claimed receptors are supported by an art-recognized utility. The present application recites that the present invention is useful, *inter alia*, in the diagnosis and treatment for diseases or disorders relating to sexual dysfunction or hormonal disorders.

The claimed receptors share at least 97% sequence homology with GREAT receptors, an LGR (Leucine-Rich Repeat-Containing G Protein-Coupled Receptor). Such receptors were known in the art prior to the filing date of the present invention (see, for example, Hsu *et al.*, Mol. Endocrinology, 14(8):1257-1271 (2000); copy attached hereto). LGRs are glycoprotein hormone receptors. Mutations in the LGRs and, in particular, in the GREAT receptor have been linked to crytorchidism, one of the most frequent congenital malformations. Crytorchidism causes infertility in adulthood and an increased risk of testicular malignancy. (Gorlov, page 2309). The LGR receptor is also said to be activated by the hormone relaxin. Relaxin activation of the LGR receptor is thought to play a role in reproductive functions. (*See*, Hsu *et al.*) Relaxin receptors were also known to the art-skilled prior to the filing date of the present application. (*See*, Bullesbach *et* al. (I); J. Biol. Chem., Vol. 267, No. 32, 22957-22960,1992; Bullesbach *et* al. (II), J. Biol. Chem. Vol., 275, No. 45, 35276–35280, 2000; copies attached hereto).

Applicant further note that products relating to the claimed receptor are commercially available. For example, Phoenix Pharmaceuticals, Inc. sells antibodies specific for several LGRs, including LGR7 and LGR8, as well as labeled hormones that bind to the receptors (*see*, attached product sheets). Biodesign sells antibodies against human relaxin I and II *see*, attached product sheet). The fact that companies make and sell such products proves that there is a well-established utility for the presently claimed receptors. Accordingly there could be no better proof of the utilities of the claimed receptors - such products are made by a manufacturer (who expects to sell them) for

consumers (who expect to buy them). Any argument that there is no art-recognized utility for such receptors seems to place the Patent Office in direct conflict with the established practices of industry.

The Utility Examination Guidelines also require a claimed invention to have a utility that is specific to the subject matter claimed (a "specific utility"). The present application recites, for example, that the claimed invention can be used, *inter alia*, to treat and/or diagnose sexual dysfunction or hormonal disorders. Thus, there is no question that Applicants have asserted at least one specific utility and, in fact, have provided numerous specific utilities for the receptors of the present invention.

As discussed above, the Office attempts to differentiate DNA ligases from GPCRs. Applicants do not agree with the Examiner's assertions. The Examiner indicates that all DNA ligases generically ligase DNA, but then states that GPCRs have "extremely diverse functions." The Office appears to be comparing apples and oranges. All GPCRs transduce a signal. In the case of the presently claimed receptors, the second messenger resulting from the transduction is cAMP. Such a utility is just as practical as the "well-known" function of DNA ligases discussed by the Examiner and referred to in the Utility Training Materials. There should be no need to provide additional information about them. A person of ordinary skill in the art need not guess whether the presently claimed GPCR conveys a practical benefit. Nor is it necessary to know how or why any given GPCR works. It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989).

Further, Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532. The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles

and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762. The Office has failed to provide proof of "total incapacity". That the claimed receptors are at least 97% homologous to known receptors with known functions certainly supports a "substantial likelihood" of utility.

Substantial Utility

In addition to conferring a specific benefit on the public, the benefit must also be "substantial". *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980).

Applicants teach, as described above, that the claimed invention can be used for the treatment and/or diagnosis of hormonal disorders or sexual dysfunction. Thus, it is clear that the claimed invention has real-world uses. All the uses described in the present application are real-world uses and, again, stand in stark contrast to the "throw away" uses (*e.g.*, landfill component or snake food) set forth in the utility guidelines. Thus, there is no question that Applicants have asserted at least one substantial utility and, in fact, have provided numerous substantial utilities. Accordingly, Applicants have complied with the substantial utility requirement.

GPCRs which have high homology to known receptors having known functions stand on a very different basis than inventions having dubious utility or function based purely on speculation. As discussed, there are a number of specific, substantial and credible utilities for the claimed receptors.

The Claimed Invention Has A Credible Utility

In addition to a specific and substantial utility, the Utility Examination Guidelines require that such utility be "credible" (a "credible utility"). The asserted utilities are credible. Clearly, the claimed polypeptides are not asserted to be a universal cure for cancer or represent a treatment for baldness. Again, as discussed, the fact that the polypeptides encoded by the claimed receptors share 97% sequence identity with a

known receptor supports the assignment of the same specific, substantial, and credible utility shared by GREAT/LGR receptors to the claimed receptors.

Applicants have demonstrated a "substantial likelihood" of utility by showing a "reasonable correlation" between the utility of the known compositions (GREAT/LGR receptors) and the composition being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565 (Fed. Cir. 1996). The Office has neither provided evidence nor sound scientific reasoning that one skilled in the art would doubt the "reasonable correlation" advanced by Applicants. Accordingly, under *Brana*, the Patent Office ***must*** accept the utility asserted by Applicants.

Prior Art Cited by Examiner Confirms the Utility of the Claimed Invention

Applicants note that the Examiner has apparently acknowledged that related receptors disclosed in prior art applications have a "specific, substantial, and credible asserted utility, or a well established utility." As discussed in greater depth below, the Office has levied a 35 U.S.C. § 102(b) rejection over the Chen *et al.* reference and the Paszty reference. Preliminarily, Applicants remind the Office that as set forth in M.P.E.P. 2121, "prior art is presumed to be operable/enabling."

In the Office Action dated July 17, 2003, the Examiner rejected claims under 35 U.S.C. § 112, first paragraph because "the claimed invention is not supported by either a specific, substantial or credible utility." The use of the Chen *et al.* reference and the Paszty reference as § 102(b) references, however, confirms that the Office considers that the cited references provide "a specific and substantial asserted utility or a well established utility". The present disclosure provides proof of utility regarding the claimed invention that is similar to the utility disclosed in Chen *et al.* reference and the Paszty reference. Accordingly, the receptors claimed in the present application provide "a specific and substantial asserted utility or a well established utility".

Other References Cited by the Office

The Examiner asserts that certain cited references prove that "function cannot be predicted solely based on structural similarity to a known protein" (Office Action, page 6). Applicants disagree with the Examiner's analysis of the references.

Doerks *et al.* (Trends in Genetics, 14:248-250, 1998) does not say that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Doerks discusses faulty characterization of UPFs (uncharacterized protein families). By definition UPFs contain members in at least 3 taxonomically and phylogenetically distinct species and do not contain biochemically-characterized proteins. Using, *inter alia*, sequence homology, Doerks was able to provide functional annotation for "more than 700 of the 1300 proteins clustered in 25 of the 58 distinct UPFs. . . . , for another 13 UPFs currently containing about 250 proteins, the presence of transmembrane regions was recorded. *Id.*" (Doerks, page 250). Although Doerks acknowledges that there are pitfalls to be avoided in annotating protein sequences, the fact that Doerks was able to ascribe a function to more than 700 out of 1300 proteins and to identify structural elements in another 250 proteins indicates that function ***can*** be predicted based on sequence similarity.

Smith discusses sequence annotation. Although Smith does indicate that there are cases where proteins with very different functions share "significant sequence similarity", Smith does not say that sequence similarity can not be used to assign function reliably. Indeed, Smith does not address the situation where, as in the present application, two receptors share over 97% homology. Instead, Smith states that the major problem with sequence annotation is "minor database annotation inconsistencies (and a few outright errors)". As discussed above, the present receptor shares at least 97% homology with at least two receptors, making the "minor database annotation inconsistencies" appear even less likely. Smith further notes that "most database annotation inconsistencies make little difference in the search for new, even distant members."

Brenner (Trends in Genetics, 15:132-133, 1999) discusses "Errors in genome annotation". Although Brenner alleges that there are problems with inferring function

from homology, the data presented does not support the Office's position that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Instead Brenner supports the use of sequence-function prediction. Indeed, on reviewing Table 1 on page 133, it appears that the highest "minimum error rate" in annotating genes was calculated to be 15%. If this is to be believed, it must be assumed then that at most, 85% of the annotations were correct and, therefore, that it ***is*** possible to ascribe function based on homology.

Yan (Science 2000, 290:523-7) discusses isoforms of ectodysplasin that differ by two amino acids. Yan, however, does not support the Examiner's assertion that function cannot be based on structural similarity. Indeed, upon a close reading of Yan, even though the isoforms have differences in binding specificity, the overall function of the isoforms is the same. Each isoform "plays a role in epidermal morphogenesis." (pages 523 and 526). Each isoform activated NF-KB (pages 524-5). Based on Yan, it ***is*** possible to ascribe a function of a molecule based on sequence similarity.

As discussed above, under *Brenner* case law, Applicants need only prove a "substantial likelihood" of utility. Certainly, the references cited by the examiner do not state that functional homology cannot be inferred by a reasonable probability. Indeed, the cited cases indicate that function ***can*** reasonably be inferred based on homology.

Summary of 35 U.S.C. § 101 Issues

The Utility Examination Guidelines note that an Examiner's "*prima facie* showing ***must*** establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial." "If the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do ***not*** impose a rejection based on lack of utility." Applicants have asserted that the claimed receptors are useful, *inter alia*, to diagnose/treat hormonal disorders and/or sexual dysfunction. As discussed the claimed receptors share over 97% sequence homology

with GREAT/LGR receptors, receptors known to be involved in hormonal disorders and sexual dysfunction. The fact that the claimed receptors share such sequence homology with known receptors supports the assignment of the same specific, substantial, and credible utilities of GREAT/LGR receptors to the claimed receptors. The utilities asserted are by Applicants art-established: those skilled in the art would readily acknowledge that the claimed receptors are useful within the meaning of 35 U.S.C. § 101.

As the present invention provides a similar degree of identification of the claimed sequences to that set forth in the cited references, the Examiner's assumption that the cited references are enabling and disclose operable GPCRs must be applied to the present invention. Further, the Examiner's statement is further proof of the art-established utilities of the presently claimed receptors.

A patent examiner ***must*** accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The Guidelines make clear that when a patent application claiming a nucleic acid, for example, asserts a specific, substantial, and credibility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility ***must*** be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. The Office has failed to provide any evidence, less still a preponderance of the evidence, to cast doubt upon any of the asserted utilities. The Office has also failed to provide any evidence that the asserted utilities are "throwaway utilities" or that the claimed polypeptides are inappropriate or unsuited for the several asserted utilities. Finally, even assuming *arguendo* that the asserted utilities are not specific or substantial, the art established utilities for the claimed polypeptides satisfy the Utility requirement of § 101.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be withdrawn upon reconsideration.

Rejections under 35 U.S.C. § 112

Claims 1-21, 25-29 and 67-72 remain rejected and new claim 80 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to adequately teach how to use the instant invention. According to the Office, "since the claimed invention is not supported by either a specific, substantial or credible utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention ..." (Office Action, page 6). The Office further asserts that:

> even if the specification taught how to use the nGPCR-1079 polypeptide, enablement would not be commensurate in scope with the claims, which encompass nucleic acids of SEQ ID NO:1, nucleic acids encoding SEQ ID NO:2, and variants thereof (% variants, allelic variants, and hybridization variants, claims 1, 3, 67, 69 and 80 for example). ... Further, the specification does not clearly define any functional domain or region in nGPCR-1079, nor, in fact, has any specific biological activity been disclosed fir nGPCR-1079. Without knowing what the biological activity is, one skilled in the art would not be able to test any variant for the its [sic] function, and it would require undue experimentation to make a variant conserving the biological activity. Additionally, the skilled artisan would not know how to use the variants encoding inactive polypeptides as there is no functional limitation associated with the variants.

(Office Action, page 7). The Office Action further alleges that Applicants' previous arguments were not persuasive because:

> the art has not established that a ⅓ fragment of a GPCR is likely to possess any functional activity, and the present application fails to demonstrate any activity associated with the nGPCR-1079. ... Additionally, the issue is not whether the assays are routine, rather, it is that one of skill in the art would not know how to make the full length or functional polypeptide and how to use the one [sic] without functional activity. With respect to the use in raising antibodies and identifying binding partners (if the fragment possessed the binding activity), as the functional activity or biological significance of the polypeptide is unknown, the issue is, once again, how to use the antibodies and the binding

> partners identified besides further research of the polypeptide itself.

(Office Action, page 8). Applicants do not agree.

As discussed above, the present invention ***is*** supported by a specific, substantial, and credible asserted utility as well as a well-established utility. One skilled in the art having read the present application would be able to make and use the claimed invention.

Preliminarily Applicants note that the claims have been amended to update specific levels of homology and further to recite functional limitations. One skilled in the art having read the present application would readily know how to make and use the claimed invention. Further, the application as filed sets forth several assays for testing whether the claimed receptors are acting as GPCRs.

Applicants also note that, as discussed above, the claimed receptors show at least 97% homology to GREAT/LGR receptors. Accordingly, the functions and activities of the claimed receptors are known. The claimed receptors and binding partners thereof would be useful in the detection and treatment of disorders relating to sexual dysfunction and hormonal disorders.

Claims 1-4, 8, 22, 27, 67, 69, 71 and 72 remain rejected and new claim 80 is also rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants do not agree.

According to the Office, Applicants' arguments were considered but not found persuasive because the specification

> fails to disclose any specific biological function associated with the protein" and "one of skill in the art would have no basis to derive the claimed ranges (variants and fragments in the instant invention) from the disclosure, and thus, would not be able to envision the detailed chemical structure of the encompassed, or to make any meaningful predictions of the useful variants and fragments of the protein.

(Office Action, page 7).

The PTO has promulgated guidelines for the application of the written description requirement in the "Revised Interim Written Description Guidelines Training Materials" (hereinafter "Written Description Guidelines"). Applicants respectfully direct the Examiner's attention to the Examples set forth therein, one of which is reproduced below:

Example 14: Product by Function
Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of A→B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.
Claim:
A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A→B.
Analysis:
A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.
A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO:3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".
The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of

> SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.
>
> A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.
>
> There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> **Conclusion:** The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

Applicants respectfully assert that the claimed invention complies with the written description requirement of 35 U.S.C. §112, first paragraph. The pending claims are analogous to the exemplary claim recited in Example 14 of the Written Description Guidelines set forth above, minus the requirement in the exemplary claim of a catalytic activity. In the exemplary claim, homologs having 90%/95%/99% sequence homology to SEQ ID NO:116 are recited. The analysis set forth in the Guidelines states that "the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must . . . have at least 95% identity to the reference sequence, SEQ ID NO: 3. . ." and that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 . . .". The Written Description Guidelines further state that "[o]ne of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the

members of the genus" and that "the disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention."

Applicants respectfully assert that the genera of proteins claimed comply with the written description requirement. The genera encompassed by the pending claims do not have substantial variation since all species within the genera must encode a GPCR polypeptide. Applicants provide a stated degree of homology (98%) which imposes a rigid structural relationship between members of the genus.

Applicants also note that functional limitations have been added to the claims. Several assays are provided throughout the specification which would allow the art-skilled to test whether such functional limitations were met.

Methods for presence determining whether a sequence shares at least 98% homology are set forth throughout the specification. As discussed above, the specification recites methods to determine whether the claimed GPCRs are in fact GPCRs. For example, page 137-150, *inter alia*, recite numerous assays that can readily be used by the art skilled to determine whether the claimed receptor is transducing a signal.

Applicants are ***not*** required to provide a specification that describes anything and everything upon which the claims could ever be construed to read. If Applicants were held to such a standard, no specification could ever be deemed to meet the written description requirement. As previously discussed, the specification adequately describes ***the subject matter defined by the present claims***, which is all that the law requires.

The Office Action has failed to provide any evidence or reasoning why the specific species described, along with a description of the attributes and features of the polypeptides that comprise the claimed genus, does not constitute adequate description of the claimed subject matter. One of skill in the art would conclude that Applicants were in possession of the necessary common attributes possessed by the members of the genera of the pending claims and that the disclosure meets the requirements of 35 U.S.C. §112 first paragraph as providing adequate written description for the claimed invention.

The subject matter encompassed by the pending claims is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Therefore Applicants respectfully request that the rejection of the pending claims under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1-21, 25-29 and 67-71 remain rejected, and new claim 80 is rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Paszty *et al.* (US 2002/0123618; "Paszty") "for the reasons of record set forth in the last Office Action, paper No. 14, at pages 10-11." Applicants do not agree.

Claims 1-9, 13, 16, 20-22, 25, 26 and 69-71 remain rejected, and new claim 80 is rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Chen *et al.* (WO 01/36471; "Chen") "for the reasons of record set forth in the last Office Action, paper No. 14, at pages 11-12." Applicants do not agree.

The crux of the rejections under 35 U.S.C. § 102 is that the cited references predate the filing date of the present invention. However, as asserted by Applicants in their previous response, the effective filing date of the present application is that of its priority application, filed August 15, 2000.

The Office alleges that the present application is not entitled to its priority date because the prior application did not satisfy the requirements under 35 U.S.C. § 101 and 112, first paragraph. However, as discussed above, the prior application does satisfy the requirements under 35 U.S.C. § 101 and § 112, first paragraph, for the reasons set forth above, and therefore is entitled to the priority date of August 15, 2000. As discussed above, the Examiner asserted references as prior art. Again, the Examiner is reminded that as set forth in M.P.E.P. 2121, "prior art is presumed to be operable/enabling."

The use of Paszty and Chen as § 102 references, however, confirms that the Office considers that the cited references provide "a specific and substantial asserted utility or a well established utility" are enabling.

Paszty discusses "Leucine-Rich Repeat-Containing G-Protein Coupled Receptor-8 Molecules and Uses Thereof" and recites "novel LGR8 nucleic acid molecules encoding a polypeptide having significant homology to the glycoprotein hormone receptor subfamily of GPCR/seven-transmembrane domain receptors." Because the Examiner alleges that Paszty anticipates claims 1-21, 25-29, 67-71 and 80 of the present application, the Office must believe that Paszty is "operable/enabling". Accordingly, because the present application provides at least as much data as Paszty, the present application ***must*** also be enabling. To hold otherwise would indicate that the Patent Office was applying the patent laws differently to different inventive entities.

Chen is directed at "Human Receptor-Associated Proteins". As set forth in the Abstract of Chen, "The invention disclosed in this patent document relates to transmembrane receptors, more particularly to a human G protein-coupled receptor for which the endogenous ligand is unknown ("orphan GPCR receptors"), and most particularly to mutated (non-endogenous) versions of the human GPCRs for evidence of constitutive activity." Chen does not recite the ligand of the claimed receptor (hRUP16). Chen further does not set forth specific functional data relating to the recited receptor. Chen does not recite a disease or disorder associated with the receptor. Nevertheless, because the Examiner alleges that Chen anticipates claims 1-9, 13, 16, 20-22, 25, 26, 69-71 and 80 of the present application, the Office must believe that Chen is "operable/enabling". Accordingly, because the present application provides at least as much data as Chen, the present application ***must*** also be enabling. To hold otherwise would indicate that the Patent Office was applying the patent laws differently to different inventive entities.

Accordingly, Applicants assert that neither Paszty nor Chen are prior art against the present application. Applicants expect that the rejections under 35 U.S.C. § 102 will be withdrawn upon reconsideration.

Rejections Under 35 U.S.C. § 103

Claims 10-12, 14, 15, 17-19 and 27-29 remain rejected under 35 U.S.C. § 103 as allegedly unpatentable over Chen *et al.* "as applied to claims 1-9, 13, 16, 20-22, 25, 26, 69-71 and 80 above" and further in view of Glucksmann *et al.*, (U.S. Patent 5,945,307; "Glucksmann") "for the reasons of record set forth in the last Office Action, paper No. 14, at pages 12-13." Applicants do not agree.

As discussed above, Chen is not prior art against the present application. Glucksmann discusses isolated nucleic acid molecules encoding a G-protein coupled receptor showing homology to the serotonin family of receptors but fails to teach or even suggest SEQ ID NO: 1 or SEQ ID NO:2. Therefore, a person of ordinary skill in the art would not have been motivated to use SEQ ID NO: 1 or 2 and combine it with the vectors, host cells and recombinant methods discussed in Glucksmann. Furthermore, even if one of skill in the art were motivated to use the Glucksmann reference, a person of ordinary skill in the art would not be in possession of the present invention because it does not teach or suggest the sequences of the present invention. Therefore, the present invention is not obvious in view of the Glucksmann reference.

In view of the foregoing, Applicant requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

The Office alleges that the instant application is not entitled to the benefit of priority of its earlier filed provisional. Applicants disagree. As discussed above, the provisional application from which the present application claims priority complies with all the requirements of the patent statutes including 35 U.S.C. § 112, first paragraph. Accordingly, the present application is entitled to the filing date of U.S. Provisional Application Serial No. 60/225,262, filed August 15, 2000.

Conclusion

Applicants believe the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6904 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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Attachments: BLAST alignment
NCBI Sequence Viewers (x2)
Gorlov *et al.*, Hum. Mol. Genet. 11 (19), 2309-2318 (2002)
Hsu *et al.*, Science 295, 5555:671-674 (2002)
Hsu *et al.*, Mol. Endocrinology, 14(8):1257-1271 (2000)
Bullesbach *et* al. (I); J. Biol. Chem., Vol. 267, No. 32, 22957-22960,1992;
Bullesbach *et* al. (II), J. Biol. Chem. Vol., 275, No. 45, 35276–35280, (2000)
Phoenix Pharmaceuticals, Inc. Product sheets for antibodies specific for LGR7 and LGR8, and labeled hormones that bind to LGR7 and LGR8
Biodesign Product sheets for antibodies against human relaxin I and II